JACC Vol. 20, No. 1
July 1992:31–5

Heparin-Induced Prolongation of Partial Thromboplastin Time After Thrombolysis: Relation to Coronary Artery Patency

JUDITH HSIA, MD, FACC, NEAL KLEIMAN, MD, FACC,* FRANK AGUIRRE, MD, FACC,† BERNARD R. CHAITMAN, MD, FACC,† ROBERT ROBERTS, MD, FACC,* ALLAN M. ROSS, MD, FACC, FOR THE HART INVESTIGATORS

Washington, D.C.; Houston, Texas; Saint Louis, Missouri

Having previously shown in the Heparin Aspirin Reperfusion Trial that the empiric use of early intravenous heparin after recombinant tissue-type plasminogen activator (rt-PA) is an important component in the overall treatment strategy, we examine in this report the specific relation between the degree of prolongation of activated partial thromboplastin time and coronary artery patency.

To evaluate the hypothesis that arterial patency after administration of rt-PA for acute myocardial infarction is sustained by effective anticoagulation, activated partial thromboplastin time of heparin recipients was determined 3 and 12 h after the start of thrombolysis. Mean activated partial thromboplastin time was higher among patients with an open infarct-related artery than in those with a closed artery (81 ± 4 vs. 54 ± 9 s, $p < 0.02$). Only 45% of patients with values <45 s at both 8 and 12 h had Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 in the infarct-related artery at 18 h. In contrast, 88% of patients with activated partial thromboplastin time >45 s and 95% of those with values >60 s had an open infarct-related artery at 18 h ($p = 0.003$ and 0.0006, respectively).

Among patients with an initially patent infarct-related artery who underwent repeat angiography at 7 days, activated partial thromboplastin time was similar in those with a persistently patent artery and those with late reocclusion. Excessive anticoagulation did not appear to increase hemorrhagic risk except that access site-related hemorrhage was more common in patients with activated partial thromboplastin time >100 s at 8 h.

These observations support the view that effective heparinization maintains coronary artery patency after thrombolysis with rt-PA.

(J Am Coll Cardiol 1992;20:31–5)

The role of antithrombins such as heparin in the maintenance of coronary artery patency after successful thrombolysis remains controversial despite the demonstration that the coagulation cascade is activated by both fibrin-specific and nonspecific thrombolytic agents (2). We have previously reported (1) that infarct-related artery patency is more frequent when intravenous heparin, rather than low dose aspirin, is given in conjunction with recombinant tissue-type plasminogen activator (rt-PA) for treatment of acute myocardial infarction. The importance of systemic anticoagulation with heparin after thrombolysis would be further supported were infarct-related artery patency more frequent in patients with definitely therapeutic levels of anticoagulation than among those with low activated partial thromboplastin times. The possible substitution of subcutaneous heparin for intravenous heparin would also be affected by any activated partial thromboplastin time-patency relation, because activated partial thromboplastin time has been reported to be close to baseline at 6 h and barely 1.5 times laboratory control value 30 h after the start of subcutaneous administration of heparin (3).

To evaluate the relation between systemic anticoagulation and the prevention of early and late reocclusion, serial activated partial thromboplastin times were determined in patients with acute myocardial infarction receiving rt-PA and adjunctive intravenous heparin; coronary artery patency was assessed at a mean of 18 h and at 7 days after initiation of thrombolysis. The relation between hemorrhagic events during hospitalization and activated partial thromboplastin time was also evaluated because intravenous heparin has been implicated as a contributor to thrombolysis-associated hemorrhage (4,5).

Methods

Study objectives. The Heparin Aspirin Reperfusion Trial (HART) included three clinical centers with eight hospitals and 24 investigators. The principal objective was to determine whether infarct-related artery patency was more frequent when intravenous heparin or oral aspirin was given in

From George Washington University, Washington, D.C.; *Baylor College of Medicine, Houston, Texas and †St. Louis University, Saint Louis, Missouri. A complete listing of participants in the HART Study Group appears in Reference 1. This study was supported in part by Genentech, South San Francisco, California. Dr. Hsia is the recipient of a Pfizer Scholars Award, Pfizer, Inc., New York, NY.

Manuscript received September 13, 1991; revised manuscript received December 9, 1991, accepted January 3, 1992.

Address for correspondence: Judith Hsia, MD, Department of Medicine, 2150 Pennsylvania Avenue, NW, Washington, D.C. 20037.

0735-1097/92/$5.00

conjunction with rt-PA during acute myocardial infarction; this analysis focuses on the group randomized to heparin therapy. The primary end points were coronary artery patency at 7 to 24 h and at 7 days. Secondary end points included recurrent ischemia (chest pain with ischemic electrocardiographic [ECG] changes or re-elevation of plasma creatine kinase levels) and hemorrhagic events, including intracerebral hemorrhage, a decrease in plasma hemoglobin of >3 g/dl due to bleeding at an identified site (excluding coronary artery bypass surgery-related blood loss) or a reduction in hemoglobin of 4 g/dl without an identified site.

Study design. Patients presenting within 6 h of onset of chest pain were eligible for entry if 0.1 mV ST elevation was identified in two contiguous leads and if none of the following exclusion criteria were present: severe hypertension, cerebrovascular disease, bleeding disorders, previous coronary artery bypass surgery, recent surgery or prolonged cardiopulmonary resuscitation, other serious medical illnesses, pregnancy or current oral anticoagulant treatment. Patients provided informed consent on a form approved by the Institutional Review Boards of the participating hospitals.

Patients received 100 mg of rt-PA (a 6 mg bolus dose, 54 mg during the 1st h, 20 mg during the 2nd h and 5 mg/h during each of the next 4 h), then were randomized to treatment with oral aspirin (80 mg/day) or intravenous heparin (5,000 IU bolus followed by infusion at 1,000 IU/h, adjusted to maintain activated partial thromboplastin time at 1.5 to 2 times the control value). Adjunctive treatment was started at the beginning of the rt-PA infusion. Infarct-related artery patency was determined 7 to 24 h (mean 18 h) after initiation of rt-PA and on the 7th hospital day. For patients assigned to heparin, the infusion rate was reduced by 50% for 2 to 3 h before catheterization. Angiograms were interpreted at the Core Laboratory by a single observer (A.M.R.) who had no knowledge of treatment arm or angiographic timing; arteries were judged closed in patients with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1 and open in patients with TIMI flow grade 2 or 3 (6).

Activated partial thromboplastin time was determined with use of Actin SS (Dade) at baseline, 8 and 12 h after initiation of rt-PA treatment, daily thereafter and 3 h after any change in heparin infusion rate.

Statistical analysis. Continuous variables are expressed as mean value ± SE. End points were tabulated and compared with chi-square or Fisher two-tailed exact test for discrete variables and by two-tailed *t* test for continuous variables. Logistic regression was used for multivariate analysis.

Results

Prolongation of activated partial thromboplastin time. A total of 205 patients were enrolled; 106 were randomized to heparin and 99 to aspirin therapy. Activated partial thromboplastin times were not required by protocol in patients randomized to aspirin therapy, but baseline values were available for 92 (92%) of 99 and for 104 (98%) of 106 patients in the heparin group. Mean values were similar in the two treatment groups at baseline, 30 ± 1 versus 31 ± 1 s for heparin and aspirin, respectively, and no different from laboratory control values. Among patients receiving heparin, activated partial thromboplastin time was significantly prolonged 8 h (76 ± 4 s) and 12 h (73 ± 4 s) after initiation of rt-PA therapy ($p < 0.001$ vs. baseline). In contrast, mean activated partial thromboplastin time at 8 h in the aspirin group was 42 ± 4 s ($n = 83$, $p < 0.001$ vs. the heparin group at 8 h).

Table 1. Patients With an Open Versus a Closed Infarct-Related Artery (IRA) at 18 Hours

	Infarct-Related Artery		
	Open (n = 78)	Closed (n = 16)	p Value
PTT(s)			
8 h	81 ± 4	54 ± 9	<0.02
12 h	76 ± 4	62 ± 10	NS
23 h	66 ± 4	58 ± 10	NS
PTT <45 s (no. [%])			
8 h	16 of 78 [21]	8 of 16 [50]	<0.02
12 h	13 of 78 [17]	7 of 16 [44]	<0.02
8 and 12 h	5 of 78 [6]	6 of 16 [38]	<0.0005
PTT >45 s (no. [%])			
8 and 12 h	54 of 78 [69]	7 of 16 [44]	0.051
PTT >60 s (no. [%])			
8 and 12 h	37 of 78 [47]	2 of 16 [13]	0.007

Patency of infarct-related arteries was determined at a mean of 18 h and partial thromboplastin time (PTT) was measured 8 and 12 h after initiation of rt-PA therapy. Values are expressed as mean value ± SE.

Coronary artery patency and activated partial thromboplastin time. Coronary angiography was performed at 18.3 ± 0.8 h after the start of rt-PA infusion in the heparin group. Five patients did not undergo angiography: one patient had a stroke, two patients refused the procedure and two were withdrawn from the study by their physicians. One additional patient is excluded from analysis because the infarct-related artery could not be identified. Among the 100 patients randomized to heparin therapy with analyzable 18-h angiograms, 94 had activated partial thromboplastin time available at baseline and at 8 and 12 h. Among patients with a closed infarct-related artery, that is, TIMI flow grade 0 or 1, the mean activated partial thromboplastin time at 8 h was lower than in the group with open arteries (TIMI flow grade 2 or 3) (Table 1).

Subtherapeutic activated partial thromboplastin time at 8 or 12 h or both 8 and 12 h was more common among patients with an occluded infarct-related artery (Table 1). Of the 11 patients randomized to receive intravenous heparin who had activated partial thromboplastin time <45 s at both 8 and 12 h, only 5 (45%) had a patent artery at 18 h. In contrast, patients with persistently therapeutic values between thrombolysis and angiography were more likely to have an open

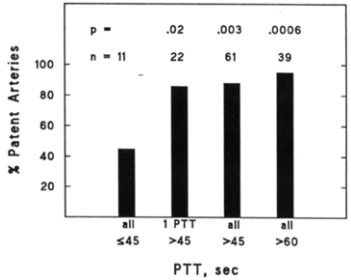

Figure 1. Infarct-related coronary artery patency and adequacy of anticoagulation. Patients received 5,000 IU of heparin as a bolus dose followed by 1,000 IU/h beginning at the start of rt-PA infusion with the goal of maintaining activated partial thromboplastin time (PTT) 1.5 to 2 times laboratory control value. "all" = activated partial thromboplastin time at both 8 and 12 h; "1 PTT" = value at either 8 or 12 h. Angiography was performed at a mean of 18 h; arteries with TIMI flow grade 2 or 3 were considered open. p values are versus the group with activated partial thromboplastin time ≤45 s at both 8 and 12 h.

artery; 54 (88%) of 61 patients with activated partial thromboplastin time >45 s at 8 and 12 h and 37 (95%) of 39 patients with a value >60 s at both times had a patent artery at 18 h (Fig. 1).

The relation between partial thromboplastin time and coronary artery patency was maintained (p = 0.025) in the presence of other variables (age, gender, clinical site, time to angiography and time to treatment); none of these variables was significantly related to arterial patency.

Partial thromboplastin time and arterial patency at 7 days. Of the 100 patients treated with heparin who had angiograms at 18 h, 82 had a patent infarct-related artery and thus were eligible for protocol angiography at 7 days. Of these 82 patients, 11 underwent coronary revascularization in the interval; 10 other patients refused (or their physician refused) the second angiogram and 1 patient died. Among the 60 patients undergoing repeat angiography, the infarct-related artery remained open in 53 and had closed in 7. Mean activated partial thromboplastin time (58 ± 1 s vs. 57 ± 4 s for open and closed arteries, respectively), the proportion of values that were subtherapeutic (202 [30%] of 682 vs. 29 [33%] of 87) and the proportion of patients with one or more subtherapeutic activated partial thromboplastin times (51 of 53 vs. 7 of 7) did not differ between the groups with an open versus a closed infarct-related artery at the second angiographic study.

Hemorrhage and partial thromboplastin time. Of the patients who received heparin, five had bleeding at puncture sites (related to angiography in three and at other access sites in two) and nine had nonaccess-related hemorrhagic events including six patients who had no identified site of blood loss, but had at least a 4 g/dl decrease in hemoglobin; one patient each had gastrointestinal, subconjunctival and retroperitoneal hemorrhage. Mean activated partial thromboplastin time at 8, 12 and 24 h did not differ between patients with and without hemorrhagic events (Table 2).

Table 2. Activated Partial Thromboplastin Time (PTT) and Hemorrhagic Events

	PTT(s)		
	8 h	12 h	24 h
No hemorrhagic event	75 ± 4	72 ± 3	61 ± 3
Any hemorrhagic event (n = 14)*	77 ± 4	72 ± 3	77 ± 2
At puncture site (n = 5)	95 ± 16	76 ± 16	83 ± 22
At other than puncture site (n = 8)	69 ± 16	87 ± 18	73 ± 20

*One patient with gastrointestinal hemorrhage died of myocardial infarction at 1 h of rt-PA infusion; thus, n = 8 for nonaccess site hemorrhage. Values are expressed as mean value ± SE.

Values >100 s were observed in 22 of 101 and 16 of 100 patients at 8 and 12 h, respectively, after the start of rt-PA infusion. Among patients with activated partial thromboplastin time >100 s, the proportion with any type of hemorrhagic event (5 of 22 at 8 h, 3 of 16 at 12 h and 6 of 25 at either 8 or 12 h) did not differ from that in the group with values ≤100 s. The proportion of patients with access site-related hemorrhage was greater among those with activated partial thromboplastin time >100 s at 8 h than that in the group with values ≤100 s (4 of 22 vs. 2 of 78, p = 0.02 by Fisher exact test). By 12 h after initiation of rt-PA therapy, the relation between access site hemorrhagic events and activated partial thromboplastin time was no longer apparent.

Discussion

The major finding in this study is the strong relation between activated partial thromboplastin time during the interval between thrombolysis and coronary angiography at 18 h and the frequency of infarct-related artery patency: 45% in patients with activated partial thromboplastin time <45 s at 8 and 12 h, 88% in those with values >45 s and 95% in those with values >60 s. Activated partial thromboplastin time did not predict hemorrhagic risk except that access site-related hemorrhage was more common in patients with values >100 s.

Coronary artery patency at 18 h. Although the HART did not study reocclusion itself, but rather patency 18 h after the start of therapy, the reduced patency rate among patients with subtherapeutic activated partial thromboplastin time can be attributed to rethrombosis because it has been repeatedly shown that 75% to 85% of infarct-related arteries are patent at 90 min after the start of rt-PA infusion (7–9). A

relatively small number of patients were observed to have persistently subtherapeutic values, reflecting adherence by investigators to the protocol requirement that activated partial thromboplastin time be maintained at 1.5 to 2 times the control level; no effort was made in the HART to prospectively compare alternative heparin regimens or target partial thromboplastin times. If the patients are classified into two groups, those with values <2 times the control value at 8 and 12 h and those with values >2 times control, the respective patency rates are 75% and 95%. These values are consistent with the European Cooperative Study Group Heparin Trial (ECSG-6) in which angiography at a mean of 81 h demonstrated 72% of arteries to be patent in patients with inadequate heparinization, defined as at least one activated partial thromboplastin time <1.3 times baseline, with samples collected at 3, 12, 24 and 36 h; in contrast, 90% of arteries were patent in patients in whom all values were >2 times control (Verstraete M, personal communication, 1991). Further, in the TIMI II trial (10) activated partial thromboplastin times at 5 to 12 h were longer among patients with a patent than in those with an occluded infarct-related artery at angiography performed at 18 to 48 h.

Clinical sequelae of coronary reocclusion. Additional support for the importance of therapeutic heparinization in the maintenance of coronary artery patency after thrombolysis was provided by Kaplan et al. (11), who reported that recurrent ischemia after thrombolytic therapy was 6 times more likely to be associated with activated partial thromboplastin time <50 s than with values >100 s. Reocclusion has been associated with a markedly adverse outcome, whereas infarct-related artery patency has generally been associated with a more favorable prognosis (12,13). In contrast to the low 4% mortality rate in patients with reperfusion at ≤90 min and with subsequently preserved patency, the fatality rate has been reported (14) to be threefold higher in patients with early reocclusion (12.8%, $p = 0.01$), underscoring the clinical importance of appropriate adjunctive therapy after initially successful thrombolysis.

The present results also potentially affect the unresolved debate between advocates of early intravenous versus subcutaneous heparin after lytic therapy, at least with rt-PA. Reocclusion of the successfully reperfused infarct-related artery occurs predominantly during the 1st 12 to 24 h (12). We have demonstrated that maintenance of a therapeutic activated partial thromboplastin time during that interval increases coronary artery patency. Turpie et al. (3) reported that 6 h after starting administration of subcutaneous heparin (12,500 IU twice daily), the activated partial thromboplastin time was barely above control levels. At 24 h, activated partial thromboplastin time remained subtherapeutic in the majority of patients receiving 15,000 IU twice daily even after an intravenous bolus of 5,000 IU.

Activated partial thromboplastin time remained <1.5 times the control value in 25% of patients in the HART at 8 h and in 21% at 12 h despite adherence to a widely used heparin regimen. This finding is consistent with the report of Hull et al. (15) that 29% of patients receiving heparin (28,484 IU/day) had subtherapeutic levels after 24 h and it suggests that optimal preservation of patency after thrombolysis might require a more aggressive anticoagulation regimen. Any potential benefit would have to be weighed against the presumptive increase in hemorrhagic risk.

Patients in the HART who were randomized to the heparin group did not receive aspirin, an agent that might have reduced the frequency of rethrombosis. The ECSG-6, which compared heparin and aspirin (250 to 300 mg) with aspirin alone, also demonstrated arterial patency to be more common among patients with activated partial thromboplastin >2 times the control level, suggesting that the addition of aspirin to heparin will not compensate for inadequate heparinization. One possible explanation for these observations is that aspirin does not inhibit thrombin-mediated platelet aggregation, and thrombin is thought to be the primary local stimulant to aggregation in this clinical setting.

Patency at 7 days. In contrast to the findings at 18 h, the extent of anticoagulation after 18 h did not affect patency at 7 days, an observation consistent with the National Heart Foundation of Australia study (16) in which 202 patients received rt-PA and intravenous heparin for 24 h, then were assigned to continue heparin or to receive aspirin and dipyridamole. Arterial patency (80%) and reinfarction at 7 days were similar in the two groups. In a smaller study, Kander et al. (17) randomized patients with TIMI grade 3 flow and without visible thrombus after either thrombolysis or acute angioplasty to receive intravenous heparin for either 24 or 72 h; patency at 1 week was the same in the two groups. Thus, although neither of these studies was definitive, they suggest that intravenous heparin is less necessary after the 1st 18 to 24 h.

Conclusions. Infarct-related coronary artery patency at any time represents a snapshot of a dynamic event involving dissolution and reformation of intracoronary thrombus. There has been a suspicion that nonfibrin-specific activators such as streptokinase, which induce high levels of anticoagulant fibrinogen and fibrin degradation products, may be less dependent on adjunctive measures to prevent reocclusion than are fibrin-specific activators such as rt-PA. However, the validity of such assumptions has not been documented. Optimally, the most advantageous regimen for each plasminogen activator should be identified and included in trials comparing thrombolytic agents. However, as far as fibrin-specific agents are concerned, our findings add to the growing evidence that vigorous antithrombotic therapy with heparin is a necessary adjunct.

References

1. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1990;323:1433–7.
2. Owen J, Friedman KD, Grossman BA, Wilkins C, Berke AD, Powers ER.

Thrombolytic therapy with tissue plasminogen activator or streptokinase induces transient thrombin activity. Blood 1988;72:616–20.

3. Turpie AG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. N Engl J Med 1989;320:352–7.
4. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico: GISSI-2. A factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Lancet 1990;336:65–71.
5. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–60.
6. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase 1 findings. N Engl J Med 1985;312:932–6.
7. Verstraete M. Thrombolytic treatment in acute myocardial infarction. Circulation 1990;82(suppl II):II-96–109.
8. Rogers WJ, Baim DS, Gore JM, et al. Comparison of immediate invasive, delayed invasive and conservative strategies after tissue-type plasminogen activator: results of the Thrombolysis in Myocardial Infarction (TIMI) phase II-A trial. Circulation 1990;81:1457–76.
9. Topol EJ, George BS, Kereiakes DJ, et al. A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. Circulation 1989;79:281–6.
10. Tracy RP, Kleiman N, Thompson BW, et al. Relationship of coagulation parameters to patency at 18–48 hours in the Thrombolysis in Myocardial Infarction trial (abstr). Clin Res 1991;39:239A.
11. Kaplan K, Davison R, Parker M, Mayberry P, Feiereisel P, Salinger M. Role of heparin after intravenous thrombolytic therapy for acute myocardial infarction. Am J Cardiol 1987;59:241–4.
12. Simoons ML, Serruys PW, van den Brand M, et al. Improved survival after early thrombolysis in acute myocardial infarction: a randomised trial by the Interuniversity Cardiology Institute in the Netherlands. Lancet 1985;2:578–81.
13. Mathey DG, Schofer J, Sheehan FH, et al. Improved survival up to four years after early coronary thrombolysis. Am J Cardiol 1988;61:524–9.
14. Ohman EM, Califf RM, Topol EJ, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. Circulation 1990;82:781–91.
15. Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. N Engl J Med 1986;315:1109–14.
16. Thompson PL, Aylward PE, Federman J, et al. A randomized comparison of intravenous heparin with oral aspirin and dipyridamole 24 hours after recombinant tissue-type plasminogen activator for acute myocardial infarction. Circulation 1991;83:1534–42.
17. Kander NH, Holland KJ, Pitt B, Topol EJ. A randomized pilot trial of brief versus prolonged heparin after successful reperfusion in acute myocardial infarction. Am J Cardiol 1993;65:1,9–42